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Review Article

How Acute Whiplash Injuries Become Chronic: The Neuro-Biological Triad of Neuronal-Glial-Immune Cells as Culprit

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Abstract

Whiplash-associated disorder (WAD) occur when there is shifting and movement of energy, during a crash or collision, from acceleration-deceleration mechanism transferred mainly to the neck region. WAD is characterized by excessive extension-flexion movements, and/or excessive side bending of the head and neck, beyond the normal and regular range of motion.

Motor vehicle collisions account for the majority of trauma related to WAD, but there are other causes such as contact sports injuries, falls, physical and domestic abuse, and other types of traumas.

Clinically, encountering cases of chronic neck pain stemming from untreated, poorly treated, or mis-managed whiplash injuries after motor vehicle collisions has become a more common and challenging encounter. The necessity to address acute whiplash injury pain-related symptoms very aggressively, early on, and in a systematic and interdisciplinary matter is essential to avoid unnecessary and avoidable long-term sequelae.

This manuscript seeks to explain the latest neurobiological theories, interplay, and interaction of a triad of neuron-glia-immune cells in the genesis of chronic pain that potentially can also apply for chronic whiplash pain. We will exclusively deal with the chronic pain aspects of WAD. The chronicity is associated with functionality limitations and restrictions, psychological and psychosocial ramifications, financial crisis, unemployment, and in cases, prolonged disability. This causes a significant economic burden on country.

Keywords: Whiplash; Whiplash-Associated Disorder; Neck Pain; Chronic Neck Pain; Motor Vehicle Collision; Chronic Pain Syndrome; Chronic Pain; Neck Trauma; Triad of Chronic Pain

Introduction

In a striking 2010 statistics published in 2015, the U.S. Department of Transportation, National Highway Traffic Safety Administration reports there were "32,999 people killed, 3.9 million were injured, and 24 million vehicles were damaged in motor vehicle crashes in the United States". The economic burden amounted to "$242 billion. This represented the equivalent of nearly $784 for each of the 308.7 million people living in the United States, and 1.6 percent of the $14.96 trillion real U.S. Gross Domestic Product for 2010. These figures include both police-reported and unreported crashes" [1].

It is very clear this debilitating injury is more than a simple 'whiplash'; it is a syndrome that develops into a chronic 'dis-ease' with its own syndrome [2].

This manuscript will review the interplay of triad of neurons, glial cells, and immune cells in chronic whiplash pain.

Nerve injury causes glial cell activation in the dorsal root ganglion (DRG) and spinal cord and may be responsible for the transition to chronic pain. This calls for the theory of non-neuronal cells in the peripheral (PNS) and central nervous system (CNS). Cytokines are released by infiltrating macrophages, Schwann cells, and satellite glial cells possibly causing maintenance of pain [3]. Activation of these cells along with microglia, and astrocytes may contribute to pain sensitivity by releasing cytokines, leading to changes in neuronal function [3]. Local macrophages and Schwann cells trigger an immune reaction that triggers recruitment of blood-derived immune cells. Opioids may interact with immune cells as opioid receptors are expressed by peripheral immune cells with resultant immune signaling changes [3].

Proinflammatory cytokines contribute to axonal damage and stimulate spontaneous nociceptor activity[3]. This causes satellite glial cells activation, leading to an immune response in the DRG driven by macrophages, lymphocytes, and satellite cells [3].

In reviewing the available research data, we can confidently state this is a promising field in pain medicine. Understanding the molecular neurobiology behind the metamorphosis of whiplash injuries into chronic pain syndromes, has a huge potential for finding multiple therapeutic remedies at almost every step of the cascade. These findings remain at very embryonic stages and need further research and eventual clinical applications.

We base our review on relevant databases such as PubMed, Ovid-Medline, Embase, and the Cochrane Library.

No Institutional Review Board permission was obtained since this manuscript does not directly involve animals or humans.

Summary of the triad of neuron-glial-immune cells cascade

Once whiplash injury occurs, the pain journey and cascade are initiated through peripheral and central nervous system pathways. Afferent neurons sense nociceptive stimuli from the corresponding cervical spinal cord divisions [4]. CNS interneurons signal messages transported via primary somatosensory cortex of the cerebral hemisphere to efferent neurons from CNS to effector organs, such as muscles [4]. Resident and migrating immune cells release mediators that modulate glial cells that surround PNS and CNS [4]. Glial and immune cells respond to injury and modulate the function of dorsal root ganglion (DRG), trigeminal ganglion, and limbic system to change pain perception [4]. All these received data contribute to the pain cognition and perception of the individual's pain [4]. At each level and step, neurotransmitters promote signals and inputs, and neuromodulators modulate pain and its perception [4]. Theoretically, therapeutic potential can affect each step of this cascade.

To better understand the mechanisms that make whiplash pain become chronic, we must indulge, in depth, in the changes that occur in these cascades.

Neurotransmitters of pain

Prior to detailing this cascade, it behooves us to remind the readers that research has shown that microglial P2X4R signaling in the spinal cord, as it relates to chronic pain, has revealed major sex differences [5]. These differences in microglial and P2X4R signaling also potentially applies to other pain conditions as well as non-spinal regions [5].

Mediators for chronic pain can be divided into 3 main categories: primary, secondary, and tertiary mediators.

- **Primary mediators:** Injuries results in activation of primary mediators that include cytokines, neuropeptides, chemokines, Wnt ligands, and growth factors. Injuries promote a Wallerian degeneration of severed axons, neutrophils and T-lymphocytes influx, macrophages, fibroblasts, Schwann cells, and mast cells [6,7]. The trigger of primary mediators cause changes in gene expression, enhance post-translational modification of proteins, and changes in ion channel status in primary afferent neurons, leading to release of secondary mediators [6,7].
- **Secondary mediators:** Primary afferent terminals in the spinal dorsal horn release secondary mediators like colony stimulating factor 1 (CSF-1), chemokine (C-C motif) ligand 21 (CCL21), and wingless-type mammary tumor virus integration, member 5A (Wnt5a). These influence spinal microglial cells causing them to release tertiary mediators [6,7].
- **Tertiary mediators:** Derived from microglia, tertiary mediators include Brain Derived Neurotrophic Factor (BDNF), Tumor Necrosis Factor- α (TNF- α), and interleukin-

1β (IL-1β). These promote excitatory transmission and decrease inhibitory synaptic transmission in the superficial dorsal horn [6,7]. Tertiary mediators along with synaptic plasticity promote the movement of nociceptive information and enhance information leading to central sensitization at supra-spinal and spinal levels [6,7]. Persistent change in microglial function leads to long-term changes in astrocyte function and hence chronic neuropathic pain [6,7].

Neurotransmitters mediate movement of impulses across the synapses [8]. This is initiated by the release of neurotransmitters from the presynaptic neuron into the synaptic cleft, binding to receptors on postsynaptic neurons [8].

Neurotransmitters can also be classified based on their function (excitatory or inhibitory), type (inflammatory mediators, including prostaglandin E2, adenosine triphosphate, adenosine, histamine, glutamate, and nitric oxide (NO), non-inflammatory mediators, including CGRP, GABA, glycine, peptides, and cannabinoids), or molecular size (large molecules, like peptides, or small molecules like amino acids and monoamines) [8].

Glial cells such as microglia and astrocytes, release various neurotransmitters that contribute to the development and maintenance of chronic pain by activating or deactivating nociceptive neurons in the CNS [9].

Pain pathways involved in whiplash injuries

Pain pathway mechanisms are very complicated cascade of events activated as a protective response to noxious stimuli. These impulses are transmitted from nociceptors by primary afferent Aδ and C fibers. These cells have bodies located in the DRG and synapse with neurons in the spinal dorsal horn [10,11]. Neurotransmitters like CGRP, glutamate, and substance P are released as part of signal transduction [10,11]. Primary nociceptive afferents synapse onto neurons in the Rexed laminae I and II and link with neurons in the dorsal horn, which are crucial in signaling the presence, severity, and location of pain [10,12]. From the dorsal horn, signals travel in the lateral spinothalamic tract to the ventral posterolateral nuclei of the thalamus [10]. The outcome is conveyed to the somatosensory cortex and periaqueductal gray matter (PAG) [10,13].

Nociceptive information is then transmitted to cortical regions responsible for memory and affective aspects of pain, such as the PAG, amygdala, nucleus accumbens (NAc), hypothalamus, and through the spinoreticular and spinomesencephalic tracts [10,13]. These cortex regions, including the somatosensory cortex, amygdala, PAG, hypothalamus, and NAc, are associated with supraspinal responses of pain pathways [10,14]. Descending pain modulatory systems involve the PAG and rostral ventral medulla (RVM) that is considered to be a major output locus in the descending modulation of nociception. It receives input from the PAG and conveys bilateral projections to the dorsal horn, ending in multiple levels and areas [15].

As far as central sensitization pathways are considered, these are triggered by enhanced nociceptive input because of inflammation and/or injury [16]. It is the product of neuroplasticity and long-lasting alterations in the CNS [16]. The mechanism of central sensitization involves glutamate signaling via postsynaptic N-methyl-D-aspartate (NMDA) receptors, which once activated, result in engaging ion channels and calcium influx [17]. This latter influx is essential in synaptic plasticity in both excitatory and inhibitory synapses. Synaptic plasticity can prime the central nociceptive system, resulting in persistent chronic pain and hypersensitivity [17].

Chronic whiplash injuries and changes in the corticolimbic system

The corticolimbic system is a mediator of chronic pain and is crucial in the development, maintenance, and amplification of chronic pain [10,18]. In addition to functional, anatomic, and structural changes, plasticity takes place in the corticolimbic circuitry when pain is transitioning from acute to chronic pain [19]. When these nociceptive signals persist, the corticolimbic circuitry stays on alert and gets activated [19].

There are multiple regions that constitute the corticolimbic structures associated with chronic whiplash pain. These structures undergo changes with injuries. These include regions such as the amygdala, periaqueductal gray (PAG), anterior cingulate cortex (ACC), hippocampus, medial prefrontal cortex (mPFC), and nucleus accumbens (NAc) [19]. We will briefly review each of these structures and enumerate their location and function.

Medial prefrontal cortex

Located in the frontal lobe, this region plays an essential role in top-down cognitive control over emotion-driven behaviors via processes including fear conditioning and extinction [20].

The prelimbic and infralimbic mPFCs receive inputs from the basolateral amygdala (BLA), hippocampus, thalamus, and contralateral mPFC. mPFC send excitatory projections to the amygdala [20]. The prelimbic mPFC predominately targets the BLA, whereas the infralimbic cortex targets BLA and lateral amygdala (LA), intercalated cell mass of the amygdala (ITC), and possibly to the lateral central nucleus of the amygdala (CeL) [21].

Amygdala

Closely located to the hippocampus, in the frontal portion of the temporal lobe, the amygdala is particularly involved in emotions and affective disorders [20].

Thalamic and cortical signals are conveyed to the amygdala, and the LA/BLA complex of the amygdala and adds emotional and affective context to sensory information [10,22]. This gathered input is relayed to the central nucleus of the amygdala, through GABA-mediated neurons and results in the regulation of fear and pain [10,22].

In one study, it was found that abnormal amygdala function was found to increase the risk of genesis of chronic pain as increased white matter connectivity within the mPFC-amygdala-hippocampus circuit and reduced amygdala size were found to be independent risk factors for chronicity of back pain [20,23].

Anterior cingulate cortex

This limbic structure is located in the frontal part of the cingulate cortex and is thought to have a role in the affective/motivational rather than sensory/discriminative aspects of pain, and in emotion, autonomic regulation, pain processing, attention, memory and decision making [10,20,24].

The medial thalamus sends nociceptive signals to ACC, along with motivation and affective information received from other areas of the brain, like the insular cortex, mPFC, and BLA [10,24]. The ACC then generates affective and motivational pain responses through its extensions to the NAc, amygdala, and mPFC [10,25].

ACC plays a crucial role in the affective dimension of pain translated mainly by the feeling of unpleasantness and secondarily by the chronic suffering from pain [26]. Such characteristics of pain contribute to shaping eventual pain-related behaviors and "reflect aversive and motivational aspects of pain". The ultimate result is that pain-related aversion leads to "behavioral avoidance or extinction of behaviors associated with noxious stimuli" [26].

Periaqueductal gray matter

PAG is located around the cerebral aqueduct within the tegmentum of the midbrain [10]. Its functions include autonomic duties, motivated behavior, behavioral responses to threatening stimuli, and acts as a primary control center for descending pain modulation [10].

PAG role reaches to the rostroventral medulla, which sends descending inhibitory and excitatory fibers to the dorsal horn of the spinal cord [10,26]. PAG encompasses processed information obtained from higher centers of the brain and receives ascending nociceptive signals from the dorsal horn of the spinal cord [8,10]. The PAG "regulates the processing of nociceptive information in the dorsal horn of the spinal cord and plays a critical role in the descending modulation of pain" [8,10].

Also, it was recently found that dopamine neurons in the ventrolateral PAG, along with dorsal raphe, differentially regulate pain-related behaviors differences in males/female mice via projections to the bed nucleus of the stria terminalis (BNST) [27]. These projections to the BNST drive sex-specific responses to pain through dopamine signaling, providing evidence of a novel ascending circuit for pain relief in males and contextual locomotor response in females [27].

Since PAG is essential in pain signaling, it is organized into four columnar subdivisions of which the dorsolateral/lateral (dl/lPAG) and ventrolateral (vlPAG) regulate responses to nociceptive inputs [28].

In a recent study involving functional MRI scans seeking to emphasize the role of PAG, and since we know noxious events potentially can cause physical harm are perceived as threats, and PAG ensures survival by generating adequate responses to these threats, [29] the study established two PAG columns implicated in pain processing that are responsive to the *threat* of experiencing pain, dl/lPAG and vlPAG. Their activation patterns indicate the regions more responsive when the incoming noxious stimulus is expected to be high or when its intensity is unknown [29].

Hippocampus

As part of the limbic system, it is located in the medial temporal lobe, the hippocampus is responsible for consolidation of memories, emotion, navigation, spatial orientation, and learning [10].

Hippocampal neurogenesis contributes to memory and learning and is implicated in the genesis of chronic pain. Studies showed that hippocampal neurogenesis upregulation resulted in the prolongation of chronic pain, and downregulating neurogenesis reversibly blocked or decreased persistent pain, and was able to dissociate the negative mood from persistent pain [30].

In a recent multicenter morphological study with emphasis on hippocampus, scientists investigated whether sex changes would be reflected on the shape of subcortical regions as related to chronic pain [31]. Hippocampus was the central focus since it is hormone-dependent on its functions. It was found that its left anterior part underwent deformation in women with chronic back pain in both United States with validation in Chinese females [31]. The study concluded that in women, that part of the hippocampus undergoes anatomical changes with pain persistence [31]. This demonstrated "sexually dimorphic involvement of emotional and episodic memory-related circuitry with chronic pain" [31].

Another study emphasized that hippocampus may play a role in both chronic pain and depression [32]. It was found that hippocampal volume reduction is related to reduced neurogenesis and neuroplasticity in cases of chronic pain and depression [32]. An increase of proinflammatory factors and a reduction of neurotrophic factors was found to change the hippocampal neurogenesis and neuroplasticity in chronic pain and depression [32].

Increasing evidence points to the fact hippocampus is involved in chronic pain [20]. Its functional and structural changes and its connectivity to limbic-cortical structures could contribute to learning and memory deficits, and to aberrant cognitive and affective states linked with persistent pain [20].

Nucleus Accumbens (NAc)

As part of the limbic system, NAc is located in the basal forebrain. This overlooked structure is responsible for cognitive processing of motivation, reward, reinforcement learning, aversion, and has a powerful role in addiction [20].

Outside the context of whiplash injuries, in a longitudinal study for patients with back pain, a small percentage of patient continued to complain of long-term pain, transitioning to chronic pain, brain-imaging changes in NAc circuitry were predictive of the transition to chronic pain [20,33]. At the time of entry into that study, strength of synchrony between the medial prefrontal cortex and NAc was predictive (>80% accuracy) of individuals who subsequently transition to chronicity one year later [33]. Thus pain-related changes in NAc cortical connectivity are found as one of the known risk factors for transition from acute to chronic pain [33,34].

In an observational study published in 2016, it was found that higher incidence of white matter and functional connections within the dorsal medial prefrontal cortex-amygdala-accumbens circuit, as well as smaller amygdala volume, represented independent risk factors, accounting for 60% in total of the variance for pain persistence [34]. The study concluded that persistence of chronic pain is predetermined by corticolimbic neuroanatomical factors [34].

The NAc is strategically located for pain signaling, as it receives innervation from both the prefrontal cortex and limbic regions (e.g., the hippocampus and amygdala), and projects signals forward to motor regions [35,36]. NAc thus plays a direct role in the modulation of pain processing via cortical circuitry and chemical neurotransmission [35].

Components of the triad

We will now review, in depth, each component of the triad constituents.

Neuronal cells

DRG is made of an axon with 2 branches, for proximal and distal processes. This conveys sensory information obtained from proprioceptors, thermoreceptors, chemoreceptors, nociceptors, to the CNS [37]. The mechanism triggers release of neurotransmitters involved in pain signaling [4]. Since DRG plays an active role in both acute and chronic pain, it changes its morphology accordingly. DRG regulates nociception before passing to the brain since most first-order neurons lay within it, causing altering of its function

and pain perception [4,38]. and triggering nociceptive G protein-coupled receptors to become expressed [4]. DRG neuron damage is associated with chronic pain conditions and neuropathies, in part due to the fact C fibers in DRG interact with thermomechanical receptors, releasing several peptidergic modulators such as substance P and calcitonin gene-related peptide (CGRP) [4,39,40].

Part of the neuronal cell clusters are ganglions. The largest sensory ganglion is the trigeminal. It transmits information from the face, head, and the jaw to the brain. This ganglion contains three branches: ophthalmic, maxillary, and mandibular [1].

Glial cells

Glial cells are the most abundant cells in the CNS. They are divided into 2 types, microglial cells (constitute up to 10% of glial cells) and macroglia that include astrocytes and oligodendrocytes [41,42]. Unlike neurons, glial cells do not convey nerve impulses. When non-activated, their function is more of auxiliary maintenance, policing, and regulation of the neuronal microenvironment. They help in the scavenging of dead neurons, regulation of the brain vasculature and blood-brain barrier. Once activated, glial cells do become "short-tempered", causing detrimental chronic pain issues [41].

There are 4 identified types of pathway states of glial activation: (1) glial reaction with concurrent upregulation of glial markers such glial fibrillary acidic protein (GFAP) and IBA1 and hypertrophic proliferation and modification of glial networks, (2) phosphorylation of mitogen-activated protein kinase (MAPK) signal pathways, (3) upregulation of adenosine triphosphate (ATP) and chemokine receptors and downregulation of glutamate transporters, and (4) synthesis and release of glial mediators such as cytokines, chemokines, neurotrophins [41,43].

Activation of glial cells can be monitored by their expression of specific markers and kinases, changes in their morphology, and the release of specific immune substances [41,44].

Satellite glial cells

Satellite glial cells (SGC) are glial cells that cover the neuron cell bodies in ganglia of the peripheral nervous system. SGC are well located to envelope sensory neurons within the spinal and trigeminal ganglia. In a sense, they act like astrocytes by keeping a check on neuronal activity and exert regulatory functions [41,45].

A study conducted by Pertin and team, found that following a nerve injury, SGC upregulate the synthesis of neurotrophins acting both as promoters of sympathetic sprouting within the ganglion[46] and as direct sensitizers of nociceptive neurons [47].

Astrocytes

Abundantly present in CNS, and activated by injury, these cells are regulators of chronic pain and are divided into A1 and A2 [48]. Astrocytic activation takes place late in the injury course, compared to microglia. Once activated, astrocytes move to the affected site, multiply, and promote scar formation via activation of the integrin-N-cadherin pathway [49]. "Inhibition of astrocyte activation can reverse or reduce chronic pain" [50].

Schwann cells

Schwann cells share some properties of SGCs and astrocytes. Considered as initial cellular detectors of injury, these cells release important mediators involved in chronic pain [51].

The principal glial cells of the peripheral nervous system are the Schwann cells [41]. In myelinated neurons, Schwann cells form the myelin sheath. Non-myelinating Schwann cells are involved in maintenance of axons and are crucial for neuronal survival. Schwann cells forming myelin sheath around A-fibers and non-myelinating Remak bundles around nociceptive C fibers do react to peripheral insults. Schwann cell activation results in modification of myelin properties altering the conduction properties of nociception [52].

Immune cells

There are multiple types of immune cells that play a role in chronic pain: mast cells, activated macrophages, neutrophils, and T lymphocytes [53].

- **Mast cells:** are considered 'first responders of the immune system". They contain many granules that are rich in a large number of bioactive substances. Mast cells release the granules content upon activation. These contain histamine, proteases, serotonin, cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1,3,4,5,6 and TNF-α, and chemokines such as CC chemokine ligand (CCL)1, CCL2, CCL3, CCL4 [54].

- **Neutrophils:** In response to tissue injury, neutrophils infiltrate tissues from the blood. They release inflammatory mediators such as interleukins, prostaglandin E2 (PGE2) and TNF-α, that can sensitize the nociceptive neurons, but their role is still unknown [55]. Studies found that inhibiting neutrophil accumulation can decrease pain after inflammation [56].
- **Activated Macrophages:** Like other types of immune cells, activated macrophages can release many inflammatory mediators such as IL1, NGF, and TNF-α sensitizing the nerve [53].
- Macrophages play a crucial role in the genesis of pain and constantly communicate with nociceptors. They release pro-inflammatory mediators that induce pain via direct activation of nociceptors. In return, research has shown that nociceptors secrete neuropeptides and chemokines which act on macrophages [57].
- **Helper T cells:** T cell subtypes cause either pro and/or anti-inflammatory cytokines and therefore may have both an excitatory and/or inhibitory outcome in chronic pain[4] depending on T cell subtypes. Research has shown that 'Helper T cells 1' are more likely to increase pain, while 'Helper T cells 2', Treg, and CD8+ T cells are protective [58]. T cells release a variety of mediators such as pro- and anti-inflammatory cytokines, endogenous opioids, and proteases to regulate pain. This regulation is either directly on pain neurons or indirectly through modulation of neuroinflammation [58].
- **Natural Killer Cells (NK):** There are hypothetical data suggesting NK cells may have a role. Studies have found that patients with musculoskeletal pain have a lower percentage of NK cells in their peripheral blood than healthy patients. Treating the pain did not restore NK cell numbers [4,59].

How acute whiplash pain becomes chronic

To simply point to one mechanism that makes acute whiplash injury become chronic is a naïve thought. From the aforementioned review, this is by no means a simple mechanism.

In brief, the injury is initiated through peripheral and central nervous system pathways. Afferent neurons sense nociceptive stimuli from the corresponding cervical spinal cord divisions [4]. CNS interneurons signal messages transported via primary somatosensory cortex of the cerebral hemisphere to efferent neurons from CNS to effector organs, such as muscles [4]. Resident and migrating immune cells release mediators that modulate glial cells that surround PNS and CNS [4]. Glial and immune cells respond to injury and modulate the function of DRG, trigeminal ganglion, and limbic system to change pain perception [4].

Melemedjian and his team demonstrated that microglial functions were unrelated to inflammation [60]. He introduced a new concept of microglial cells and microglial pain. He postulates that microglial cells have a role in the initiation of chronic nociceptive sensitization, but they do not take part in maintaining a chronic pain state. He added that a ZIP-reversible process is responsible for the maintenance of persistent sensitization [60]. He emphasized on the role of BDNF in playing a major role in initiating and maintaining persistent nociceptive sensitization through a ZIP-reversible phenomenon [60]. He concluded that BDNF, through its receptor tyrosine receptor kinase type B (trkB) acts as a key regulator in PKC synthesis and phosphorylation and plays a vital role in maintenance of persistent and chronic pain [60]. This landmark finding is the first to directly demonstrate that neurotransmitter-neurotrophins relationship is related to initiation and maintenance of central chronic pain state [60].

Conclusion

In this review manuscript, we conclude, in summary, that an injury causes glial cell activation in the DRG and spinal cord and may be responsible for the transition to chronic pain. This points to a non-neuronal cell as culprit in the PNS and CNS. Cytokines are released by infiltrating macrophages, Schwann cells, and satellite glial cells possibly causing maintenance of pain. Activation of these cells along with microglia, and astrocytes may contribute to pain sensitivity by releasing cytokines, leading to changes in neuronal function. Local macrophages and Schwann cells trigger an immune reaction that in turn triggers recruitment of blood-derived immune cells. Opioids may interact with immune cells as opioid receptors are expressed by peripheral immune cells with resultant immune signaling changes.

This manuscript points that many factors including cytokines, interleukins, purines, peptides, cannabinoid receptors, sodium, and potassium channels, MAP kinases, proteases all can be targets of pain therapy. Glial and support cells are impeccable targets. The triad of neurons, glia, and immune cells is no doubt a great finding

that will hopefully guide many clinicians and researcher to aim at these targets thertapeutically.

Future Directions

The current pharmacological management of chronic pain is mostly limited to symptomatic treatment rather than disease-modifying. The current treatment is limited in efficacy and has many adverse effects. This area of molecular neurobiology pain research is ever-changing and improving. The traditional thinking that only a few areas, or structures, or elements in the brain are responsible for, or are involved in pain, pain initiation, simple transition from acute to chronic pain, and pain memory is expiring. It is becoming evident that brain has multiple peripheral and central areas involved in pain pathology and hence the cascade of events that leads to the genesis of chronic pain is multifactorial. Acting upon these changes early on may positively derail the untoward effects of chronic pain, from acting on nociceptors, to pathways, to including immunotherapy and biologic agents. Finding safe and adequate pharmacological therapeutics is warranted and moving it from bench to clinic is the goal. At each level of the pain cascade of neuronal, glial, and immune levels, the areas of therapeutics are promising. The work of many pain neurobiology researchers is crucial and very much appreciated. Without them, we are unable to advance this field to help our chronic pain patients. It is our opinion that moving these findings from experimental to plausible clinical helpful therapeutic options is closer than ever. Studies on causes of sustenance of plasticity, central sensitization, and chronic pain are amassing massive research work thanks to deep knowledge of molecular neurobiology of pain.

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